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# Home-based tuberculosis contact investigation in Uganda: a household randomised trial

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## ABSTRACT

**Introduction:** The World Health Organization (WHO) recommends household tuberculosis (TB) contact investigation in low-income countries, but most contacts do not complete a full clinical and laboratory evaluation.

**Methods:** We performed a randomised trial of home-based, SMS-facilitated, household TB contact investigation in Kampala, Uganda. Community health workers (CHWs) visited homes of index patients with pulmonary TB to screen household contacts for TB. Entire households were randomly allocated to clinic (standard-of-care) or home (intervention) evaluation. In the intervention arm, CHWs offered HIV testing to adults; collected sputum from symptomatic contacts and persons living with HIV (PLWHs) if  $\geq 5$  years; and transported sputum for microbiologic testing. CHWs referred PLWHs, children  $< 5$  years, and anyone unable to complete sputum testing to clinic. Sputum testing results and/or follow-up instructions were returned by automated SMS texts. The primary outcome was completion of a full TB evaluation within 14 days; secondary outcomes were TB and HIV diagnoses and treatments among screened contacts.

**Results:** There were 471 contacts of 190 index patients allocated to the intervention and 448 contacts of 182 index patients allocated to the standard-of-care. CHWs identified 190/471 (40%) intervention and 213/448 (48%) standard-of-care contacts requiring TB evaluation. In the intervention arm, CHWs obtained sputum from 35/91 (39%) of sputum-eligible contacts and SMSs were sent to 95/190 (50%). Completion of TB evaluation in the intervention and standard-of-care arms at 14 days (14% *versus* 15%; difference  $-1\%$ , 95% CI  $-9\%$  to  $7\%$ ,  $p=0.81$ ) and yields of confirmed TB (1.5% *versus* 1.1%,  $p=0.62$ ) and new HIV (2.0% *versus* 1.8%,  $p=0.90$ ) diagnoses were similar.

**Conclusions:** Home-based, SMS-facilitated evaluation did not improve completion or yield of household TB contact investigation, likely due to challenges delivering the intervention components.



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**In a household randomised trial in Kampala, Uganda, home-based, SMS-facilitated evaluation did not improve completion or yield of household TB contact investigation. Future studies will evaluate user-centred design to improve intervention delivery.** <http://bit.ly/2xwLpDu>

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## Introduction

The STOP TB Partnership has called for the elimination of tuberculosis (TB) by 2050, but approximately 3.6 million patients still go undiagnosed each year [1]. The majority of missing individuals with TB reside in low-income communities and many do not seek care despite persistent symptoms [2]. To help reach these individuals, the World Health Organization (WHO) issued guidelines recommending household TB contact investigation as routine public health practice in low- and middle-income countries [3]. The results of large, cluster-randomised, controlled trials show that household contact investigation increases TB diagnoses [4] and likely reduces TB transmission in the community [5] compared with passive case-finding. Nevertheless, most available evidence [6] and policies [7] do not address how contact investigation should be adapted for delivery in high-burden, low-income countries. There is an urgent need for implementation research to inform guidelines and practice [8].

We and others have identified low rates of delivery and uptake of household contact investigation in several high-burden countries where contact investigation has been introduced, with only about 25% of household contacts completing household TB screening and 20–89% of eligible contacts failing to complete TB evaluation [9, 10]. Major barriers to the acceptance and completion of contact investigation include a lack of TB-specific knowledge; TB-related stigma; travel and opportunity costs to attend clinics; and dissatisfaction with quality of clinic services [11, 12]. To address these barriers, we designed a multicomponent implementation strategy to facilitate more effective and patient-centred delivery of household TB contact investigation [12]. This strategy consisted of community health worker (CHW)-initiated TB evaluation at home, including HIV testing and sputum collection, transportation of sputum to clinics for TB testing, and communication of testing results and follow-up instructions to contacts by automated SMS texts. Initiating testing in the household adds further complexity to contact investigation, and the feasibility and effectiveness of such services is unknown. Therefore, we sought to determine whether this strategy could increase the proportion of contacts completing TB evaluation and receiving new TB diagnoses and treatments.

## Methods

### *Study design and setting*

We performed a pragmatic, prospective, household randomised trial of home-based, SMS-facilitated household TB contact investigation in Kampala, Uganda (Pan-African Clinical Trials Registry #201509000877140). The Uganda National TB and Leprosy Programme (NTLP) offers free TB evaluation and treatment services in public sector primary care clinics, and in 2013 it introduced household TB contact investigation as a routine public health service in Kampala. Working with a local nongovernmental organisation, we hired experienced, local CHWs to deliver household contact investigation and treatment support. We trained them to provide home sputum collection and HIV counselling and testing services in accordance with Uganda National Guidelines [13, 14], and reimbursed their travel expenses.

### *Study population and recruitment*

CHWs invited consecutive “index” patients diagnosed with TB at seven public sector primary care clinics to allow a home visit for CHWs to screen household members for TB at home. Index patients of any age with pulmonary TB bacteriologically confirmed by sputum smear microscopy or GeneXpert MTB/RIF testing, and young children (*i.e.* <5 years of age) clinically diagnosed with pulmonary or extrapulmonary TB were eligible. CHWs visited the homes of index patients and identified all household contacts, defined as individuals sleeping under the same roof as the index patient for ≥1 day or night within the previous 3 months. Exclusion criteria are described in the supplementary material.

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### *Study procedures including randomisation*

After obtaining written informed consent from participants or their guardians and assent from minors aged 8–17 years, CHWs collected demographic and clinical information from index patients and contacts, including answers to TB screening questions for contacts. CHWs recorded responses using a customised, Open Source, survey application (CommCare, Dimagi, Cambridge, MA, USA) wirelessly linked to a Cloud-based server. An automated decision-support algorithm within the survey application based on WHO contact investigation guidelines was used to identify contacts requiring additional clinical and/or laboratory evaluation for active TB, including those reporting at least one TB symptom (cough  $\geq 2$  weeks, fever, night sweats, or weight loss  $\geq 3$  kg), young children  $< 5$  years of age, and persons living with HIV (PLWHs) (figure S3) [3].

After all contacts had completed TB screening, household members underwent concealed, 1:1, household-level, random allocation to referral for open-label TB and HIV testing in nearby clinics (standard-of-care) or in their own homes, with sputum testing results and/or follow-up instructions provided by automated SMS (intervention). Chest radiography is not available in public sector primary care clinics in Uganda and was therefore excluded from the screening and testing algorithms [8]. Allocation was stratified by index patient age (adults  $\geq 15$  years, older children aged 5–14 years, young children aged  $\leq 5$  years), HIV status, and enrolling CHW. Additional details are available in the supplementary material.

### *Intervention characteristics*

In the standard-of-care arm, CHWs referred contacts with indications for TB testing and/or clinical evaluation to health facilities for standard sputum examination, HIV counselling and testing, and evaluation by a clinician. In the intervention arm, CHWs first offered home HIV counselling and testing to contacts aged  $\geq 15$  years, as previously described [15, 16]. After providing standardised instructions to contacts, CHWs then collected one or two expectorated sputum samples over 2 days from eligible adults and children  $\geq 5$  years. CHWs delivered sputum to clinic laboratories for serial smear microscopy and/or single-sample Xpert MTB/RIF testing according to the availability of these tests at each clinic (see Methods, Online Supplement). CHWs entered all clinical information and sputum testing results into the survey application, which applied an algorithm to characterise each contact's need for further evaluation and treatment according to pre-specified categories (figure S3). Category-specific messages reporting results and/or follow-up instructions were generated following a customised algorithm (CommCare Messaging) (figure S4) and delivered by automated SMS to participants in their preferred language using a telephone number verified during the household visit (see Online Supplement).

### *Measurements and outcomes*

The primary outcome, completion of TB evaluation within 14 days of enrolment among contacts requiring additional evaluation for TB, was determined in collaboration with internal and external stakeholders [17]. We defined completion according to WHO contact investigation guidelines, which recommend a complete sputum examination by serial smear microscopy or Xpert, and/or a clinic visit for a clinician's evaluation for young children, PLWHs, and for contacts who did not complete sputum examination [3]. Secondary outcomes included 1) TB diagnosis and treatment initiation and 2) HIV diagnosis and linkage to HIV care. We assessed fidelity through process evaluation of implementation metrics in intervention-arm contacts only, including the proportions of eligible contacts undergoing HIV testing, of eligible contacts providing sputum, and of eligible contacts to whom SMS were sent, as previously reported [15, 18–20]. We examined time to completion of TB evaluation as a *post hoc* secondary outcome. We pre-specified subgroup analyses for TB completion by age ( $< 5$  years, 5–14 years,  $\geq 15$  years) and HIV status.

### *Sample size calculations and statistical analysis plan*

We estimated that 387 household contacts per arm would provide 80% power with a Type I error of 0.05 to detect an increase of  $\geq 15\%$  in the proportion of eligible contacts completing TB evaluation, assuming 10% completed evaluation in the standard-of-care arm and a design effect of 1.7. Additional details are available in the Online Supplement.

We compared baseline demographic and clinical characteristics of index patients with TB and contacts between allocation groups using the Chi-squared test for categorical variables and the rank-sum test for continuous variables. All analyses were conducted by intention to treat, without regard to adherence to intervention components. We assessed between-arm differences in completion of TB evaluation, the primary outcome, using mixed-effects, logistic models with random intercepts to capture household clustering and robust standard errors. Regression standardisation was used to estimate the marginal probability of the primary outcome by study arm, based on parameter estimates from the logistic model. This approach was also used to estimate treatment effects on detection of TB (clinically confirmed and/or microbiologically confirmed) among all contacts screened, a standardised indicator of the yield of contact

investigation [21]. We applied the same approach to estimate the yield of new HIV diagnoses among contacts aged  $\geq 15$ . Finally, we plotted Kaplan–Meier curves for the time to completion of TB evaluation by treatment arm.

### Human subjects' considerations

This study protocol was approved by the Makerere School of Medicine Research Ethics Committee, the Uganda National Council for Science and Technology, and the Yale University Human Investigation Committee.

## Results

### Index patient enrolment

From July 2016 through July 2017, 14 CHWs screened consecutive index patients for eligibility (figure S1) and enrolled 471 for household visits. Household visits were not completed for 99 (21%) patients, leaving 372 (80%) index patients whose households were visited.

### Household contact enrolment

The 372 index patients reported 1228 household members living with them. During household visits, CHWs screened 1193 (97%) household members for eligibility (figure 1). Of these, 274 (23%) did not meet the eligibility criteria (figure S2), resulting in 919 (77%) enrolled contacts who were screened for TB symptoms and risk factors. We stopped the trial upon exceeding the enrolment target.

### Study population

Of 372 index patients whose households were visited, household contacts of 190 (51%) index patients were randomised to the home-based, SMS-facilitated TB evaluation arm and household contacts of 182 (49%) index patients to the standard-of-care arm. Demographic and clinical characteristics of index patients are provided in table 1.

We enrolled 471 contacts in the intervention arm, and 448 contacts in the standard-of-care arm. Demographic and clinical characteristics of contacts are provided in table 2. CHWs visited 22 (12%) intervention-arm households and 26 (14%) standard-of-care arm households twice to enrol all contacts; all other households were visited once. CHWs identified 190/471 (40%) intervention-arm contacts and 213/448 (48%) standard-of-care arm as patients eligible for further TB evaluation during screening. Most contacts intended to follow-up in the same clinic where the index patient was recruited, whether in the intervention ( $n=449$ , 95%) or standard-of-care ( $n=420$ , 94%) arm.

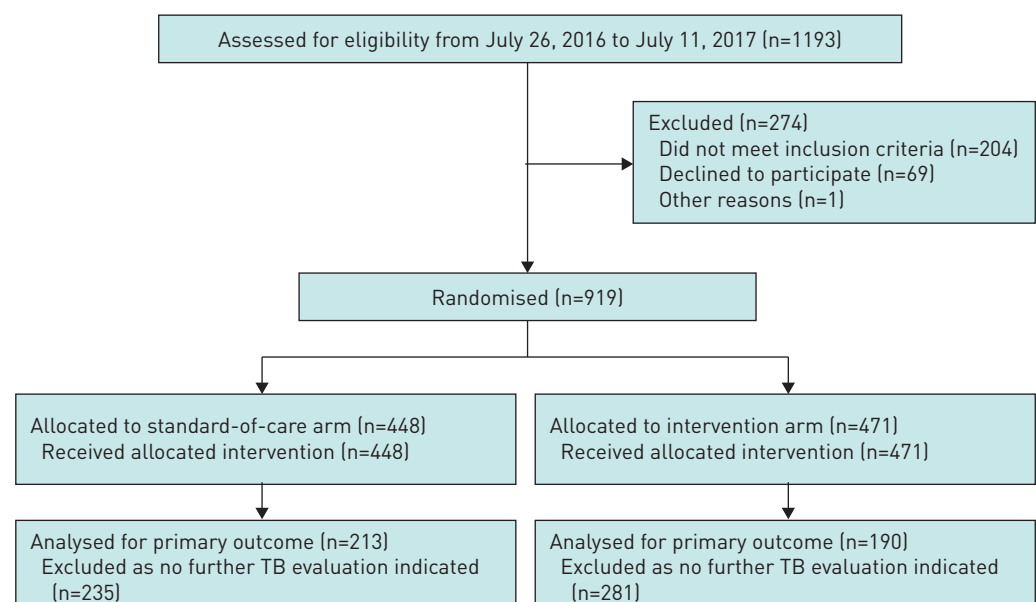


FIGURE 1 CONSORT flow diagram describing enrolment of household contacts. TB: tuberculosis.

TABLE 1 Characteristics of index patients with tuberculosis

Characteristics	Intervention arm (n=190)	Standard-of-care arm (n=182)	p-value <sup>#</sup>
<b>Age</b>			0.44
<5 years	4 (2%)	7 (4%)	
5–14 years	7 (4%)	4 (2%)	
≥15 years <sup>¶</sup>	179 (94%)	171 (94%)	
<b>Female</b>	80 (42%)	81 (45%)	0.64
<b>HIV status<sup>*</sup></b>			0.98
Positive	64 (34%)	63 (35%)	
Negative	125 (66%)	118 (65%)	
Unknown	1 (0.5%)	1 (0.6%)	
<b>Coughing time weeks</b>	4 (3–12)	8 (3–12)	0.41 <sup>§</sup>
<b>Contacts reported</b>	3 (1–4)	3 (2–4)	0.78 <sup>§</sup>

Data are presented as median (interquartile range) unless otherwise stated. <sup>#</sup>: Chi-squared test of significance unless otherwise stated; <sup>¶</sup>: age among individuals ≥15 years of age was 30 [24–38] years in the intervention arm and 29 [24–38] years in the standard-of-care arm (p=0.94 by the Wilcoxon rank-sum test of significance); <sup>\*</sup>: HIV status was unknown for one patient in the intervention arm and for one patient in the standard-of-care arm; <sup>§</sup>: Wilcoxon rank-sum test of significance.

TABLE 2 Characteristics of household contacts

Characteristics	Intervention arm (n=471)	Standard-of-care arm (n=448)	p-value <sup>#</sup>
<b>Age</b>			0.29
<5 years	95 (20%)	106 (24%)	
5–14 years	121 (26%)	121 (27%)	
≥15 years <sup>¶</sup>	255 (54%)	221 (49%)	
<b>Female</b>	293 (62%)	268 (60%)	0.46
<b>HIV status prior to screening</b>			0.15
Positive	27 (6%)	32 (7%)	
Negative	308 (65%)	265 (59%)	
Unknown	136 (29%)	151 (34%)	
<b>Any TB symptom present</b>	106 (23%)	116 (26%)	0.23
Cough for ≥2 weeks	70 (15%)	95 (21%)	0.01
Fever	32 (7%)	45 (10%)	0.08
Night sweats	28 (6%)	34 (8%)	0.32
Weight loss ≥3 kg	37 (8%)	46 (10%)	0.20

TB: tuberculosis. <sup>#</sup>: Chi-squared test of significance utilised, unless otherwise noted; <sup>¶</sup>: median (interquartile range) age among individuals ≥15 years of age was 26 [20–38] years in the intervention arm and 27 [20–36] years in the standard-of-care arm (p=0.50 by the Wilcoxon rank-sum test of significance).

### *Fidelity of home-based procedures and SMS in the intervention arm*

Among 255 intervention-arm contacts aged ≥15 years, 229 were eligible for HIV counselling and testing. Of these, 121 (53%) consented, all of whom were tested. Overall, 5 (4%) contacts were newly diagnosed with HIV at home, 115 tested negative and 1 had an indeterminate test result and was referred to the clinic for further testing. Sputum was obtained from 35/91 (39%) eligible contacts (*i.e.* contacts aged ≥5 years who had TB symptoms or were PLWHs), with 28 (80%) tested with Xpert. SMSs were sent at baseline as planned for 95/190 (50%) contacts undergoing TB evaluation; the other SMSs were never initiated because of a programming error introduced during quality assurance testing in which a subset of SMS targeting PLWHs were mistimed to the morning that evaluation status was updated (*i.e.* in the past) rather than to the following morning.

### *Completion of TB evaluation*

Summary results and subgroup analyses for primary and secondary outcomes are presented in table 3. After adjusting for household clustering, contacts had a marginal probability of completing the TB evaluation within 14 days of 14% (95% CI 8–20) in intervention households and 15% (95% CI 9–21) in standard-of-care households (difference –1%, 95% CI –9% to 7%, p=0.81); the intra-class correlation was

TABLE 3 Study outcomes, adjusted for household clustering and stratified by clinically relevant subgroups

Outcome <sup>#</sup>	Intervention arm	Standard-of-care arm	p-value
<b>Completion of TB evaluation</b>			
<5 years of age	8/95 (8%)	18/106 (17%)	0.12
5–14 years of age	11/32 (34%)	15/33 (45%)	0.41
≥15 years of age without HIV	13/32 (41%)	9/45 (20%)	0.09
PLWH	5/32 (16%) <sup>¶</sup>	4/32 (13%)	0.75
<b>Yield of microbiologically confirmed TB</b>			
<5 years of age	2/95 (2.1%)	1/106 (0.9%)	0.51
5–14 years of age	3/121 (2.5%)	3/121 (2.5%)	1
≥15 years of age without HIV	1/224 (0.5%)	1/192 (0.5%)	0.91
PLWH	1/32 (3.1%)	0/32 (0%)	0.31
<b>Yield of clinically and microbiologically confirmed TB</b>			
<5 years of age	5/95 (5.2%)	4/106 (3.8%)	0.62
5–14 years of age	3/121 (2.5%)	6/121 (5.0%)	0.38
≥15 years of age without HIV	1/224 (0.5%)	5/192 (2.6%)	0.17
PLWH	1/32 (3.1%)	0/32 (0%) <sup>#</sup>	

TB: tuberculosis; PLWH: person living with HIV. The denominator for completion includes only those screening positive by symptoms, age or being a PLWH (190 in the intervention arm, 230 in the standard-of-care arm). The denominator for yield outcomes includes all household contacts (471 in the intervention arm, 443 in the standard-of-care arm). PLWHs are also reported with the relevant age subgroups. #: assessed 60 days after contact enrolment; ¶: includes five PLWHs newly diagnosed during home HIV counselling and testing.

0.66 (95% CI 0.40–0.85). At 60 days, marginal probabilities were 20% in the intervention arm and 18% in the standard-of-care arm (difference 2.5%, 95% CI –6% to 11%,  $p=0.57$ ). Figure 2 shows the cumulative incidence of completing TB evaluation among eligible contacts stratified by allocation arm.

### TB diagnoses

The proportion of all contacts diagnosed with microbiologically confirmed TB, also called the yield of contact investigation, was similar in the intervention (7/471, 1.5%) and standard-of-care (5/448, 1.1%) arms (OR 1.34, 95% CI 0.42–4.24,  $p=0.62$ ). The marginal probability of contacts diagnosed with any form

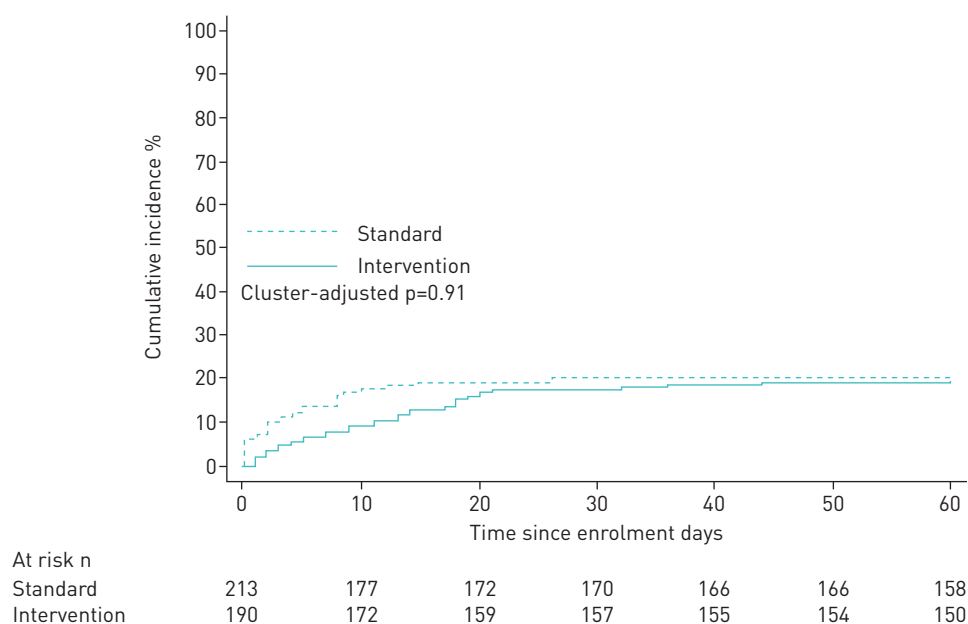


FIGURE 2 Cumulative incidence of eligible household contacts completing tuberculosis evaluation from the time of enrolment, stratified by allocation arm.



of TB, including clinically diagnosed TB and extrapulmonary TB, were similar in the intervention (2.1%) and standard-of-care (2.4%) arms (difference  $-0.2\%$ , 95% CI  $-3\%$  to  $2\%$ ,  $p=0.83$ ). All participants diagnosed with TB (25/25, 100%) were initiated on TB treatment.

### Subgroup analyses

Among contacts aged  $\geq 5$  in the intervention arm, home sputum collection was substantially more successful among contacts living without HIV (29/63, 46%) than among PLWHs (6/28, 21%,  $p=0.03$ ). The cluster-adjusted probability of completing TB evaluation within 60 days for symptomatic contacts aged  $\geq 5$  without HIV was similar in the intervention arm (39%) and the standard-of-care arm (25%, difference 14%, 95% CI  $-4\%$  to  $31\%$ ,  $p=0.16$ ).

## Discussion

Active case-finding of undiagnosed individuals with TB in settings outside health facilities is a cornerstone of the Global Strategy to End TB, which seeks to eliminate TB as a public health threat by 2050 [22]. Research evaluating bold, new, patient-centred strategies is critical to advancing toward these targets. In this study, we carried out a rigorous evaluation of a novel patient-centred strategy to improve delivery and completion of household TB contact investigation, a prototypical approach to active case-finding endorsed by WHO [3]. In a real-world public health setting, only about one in five household eligible contacts completed TB evaluation, and there was no improvement with home sputum collection and automated SMS results reporting compared with TB evaluation in clinic.

Incomplete delivery of the intervention, including a low proportion of contacts successfully submitting sputum and receiving SMS, may have contributed to its lack of effectiveness in improving completion of TB evaluation by addressing previously documented distance and financial barriers to attending clinics [12, 23]. As previously reported, contacts and CHWs reported several challenges with home sputum collection, including difficulties for asymptomatic contacts in expectorating, limited private space to expectorate indoors, and a reluctance to expectorate outside because of stigma [18]. Even symptomatic contacts often failed to expectorate on the spot, and CHWs reported that leaving sputum containers to be collected later was unsuccessful. CHWs sometimes did not carry enough sputum containers for all eligible contacts. Although trained on safe sputum collection and transport [18] and equipped with particulate respirators, CHWs expressed fears of contracting TB by collecting and carrying sputum in their work bags. Finally, because intervention households were distributed among 17 CHWs, some CHWs only rarely collected sputum, limiting the opportunities to gain proficiency. Low success rates of sputum collection have been observed in other similar settings [9], including among PLWHs [24]. Future studies should evaluate strategies to promote health worker confidence and competence in sputum collection, including delivery of instructional videos *via* phones or tablet computers [25].

SMSs were successfully initiated for only half of intervention-arm contacts undergoing additional TB evaluation. In a previous, more detailed process evaluation of SMSs, we found that  $<20\%$  of SMSs achieved their full effects, defined as being sent, delivered, read by the intended recipient, and having the message content understood and retained [19]. Participants reported several barriers to engaging with SMS, including sharing phones with friends and family; broken phones; an inability to read text messages; and a lack of familiarity with or attentiveness to SMS. Although systematic reviews suggest that two-way SMS may be more effective than one-way SMS [26], we also observed a low uptake of invitations to two-way SMS [19]. Previous SMS interventions for TB in low- and middle-income countries have mostly used SMS longitudinally for treatment support [27], rather than cross-sectionally to facilitate diagnostic evaluation as in this study, although there is evidence suggesting that transaction-focused SMS such as appointment reminders modestly increase clinic attendance in a variety of settings [28]. Participants in our study who confirmed receiving SMS stated that while they found SMS helpful, it could not replace in-person disclosure of results [29].

This is among the first randomised trials of a mobile health intervention for TB in a low-income country. As described previously, this intervention was developed with broad input from household contacts and health workers [12, 17, 30] and deployed on a widely-used, Open Source mobile survey platform. Nonetheless, we experienced substantial challenges adapting the application to the complexities of household contact investigation, a multilevel intervention requiring a series of contingent steps occurring at multiple times and locations. The logic required to generate automated SMSs was particularly complex, encompassing thousands of unique clinical and laboratory states to determine if TB evaluation was complete and send appropriate SMS content. This posed challenges for quality assurance testing that slowed identification of programming errors, including one that prevented some SMSs from being sent.

WHO has called for increased high-quality research on digital interventions for TB care [31]. Given the challenges with both patient engagement and delivery of digital interventions in this study [19, 32], there is a need to involve professional designers to improve how patients and providers interface with mobile



health interventions. User-centred design is an internationally accepted standard for quality in developing information technology applications [33]. An evolution of this approach (termed “Human-Centred Design” or generically, “design-thinking”) is increasingly being applied to build health delivery systems that ensure participant engagement through methods that prioritise the needs of end-users throughout intervention development [34, 35].

Our study had several limitations. First, we may not have captured all diagnoses of prevalent TB among patients presenting to nonstudy (or study) clinics unbeknownst to CHWs; however, we believe under-ascertainment of clinic visits is unlikely because the contacts’ clinic preferences mirrored those of the index patients, and a prior audit found clinic registers and the survey application to be highly concordant [10]. Second, although additional incident TB cases may be identified in the first 2 years after household contact screening, we did not review clinic registers for incident clinic evaluations or diagnoses of TB. We did however ask CHWs to record this information digitally, and they maintained close contact with index patients as part of concurrent treatment support activities. Third, although household TB contact investigation provides important opportunities for TB prevention through diagnosis and treatment of latent TB infection, these services are not currently standard-of-care in Uganda.

Our study also had several strengths. This is among the first studies of a patient-centred strategy to improve household contact investigation in a high-burden, low-income setting. As previously described [12, 17], we employed a stakeholder-engaged approach informed by the Behaviour Change Wheel framework and the Capability-Opportunity-Motivation-Behaviour theory to develop this implementation strategy [36], and we evaluated it in a real-world setting using both implementation and effectiveness metrics [37]. Although home-based, SMS-facilitated household contact investigation was no more effective than the standard-of-care, clinic-based contact investigation, we carried out a careful process evaluation using mixed methods to determine which components of the strategy did and did not work [15, 18, 20, 29]. As improving the quality of TB care assumes greater priority on the global TB research and programme agenda [38, 39], such multilevel, multimodal evaluations are critical to understanding the context, fidelity, and adaptability of new interventions.

Although fewer than one in five household contacts completed the TB evaluation across both study arms, the yield of prevalent, microbiologically confirmed TB was 1%, similar to that reported in a recent randomised trial in Vietnam [4]. This diagnostic yield was however lower than the 3.1–4.5% described in systematic reviews [6, 40]. Future studies should examine whether the yield of new TB diagnoses can be improved by reducing drop-out from each step of the contact investigation cascade, as demonstrated in clinic settings [41]. In addition, improving completion rates for TB evaluation increases opportunities for preventive treatment of latent TB infection among close contacts, as envisioned by new WHO guidelines [42]. The suboptimal results of implementation in this study highlight the many challenges of delivering complex, community-based interventions like contact investigation in low-income countries, even when facilitated by mobile health strategies. As the global community of TB practitioners and researchers continues its search for more effective approaches for finding and treating undiagnosed individuals with TB and preventing TB among those who have been exposed, there is critical need for research to address “know-do” gaps and equitably deliver integrated services that are safe, timely, effective, patient-centred, efficient, and affordable.

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This study is registered with the Pan-African Clinical-Trials Registry under identifier number 201509000877140. Data available from the Dryad Digital Repository: <https://doi.org/10.5061/dryad.kn4gv14>.

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## References

- 1 World Health Organization. Global tuberculosis control: WHO report 2018. Geneva, World Health Organization, 2018.
- 2 Uganda Ministry of Health. The Uganda National Tuberculosis Prevalence Survey 2014–2015 Report. Kampala, Ministry of Health, 2017.
- 3 World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva, World Health Organization, 2012.
- 4 Fox GJ, Nhung NV, Sy DN, *et al.* Household-contact investigation for detection of tuberculosis in Vietnam. *N Engl J Med* 2018; 378: 221–229.
- 5 Ayles H, Muyoyeta M, Du Toit E, *et al.* Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. *Lancet* 2013; 382: 1183–1194.
- 6 Fox GJ, Barry SE, Britton WJ, *et al.* Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; 41: 140–156.
- 7 Hwang TJ, Ottmani S, Uplekar M. A rapid assessment of prevailing policies on tuberculosis contact investigation. *Int J Tuberc Lung Dis* 2011; 15: 1620–1623.
- 8 TB CARE I. Adaptation and implementation guide for recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. The Hague, TB CARE I, 2015.
- 9 Blok L, Sahu S, Creswell J, *et al.* Comparative meta-analysis of tuberculosis contact investigation interventions in eleven high burden countries. *PLoS One* 2015; 10: e0119822.
- 10 Armstrong-Hough M, Turimumahoro P, Meyer AJ, *et al.* Drop-out from the tuberculosis contact investigation cascade in a routine public health setting in urban Uganda: A prospective, multi-center study. *PLoS One* 2017; 12: e0187145.
- 11 Fox GJ, Loan le P, Nhung NV, *et al.* Barriers to adherence with tuberculosis contact investigation in six provinces of Vietnam: a nested case-control study. *BMC Infect Dis* 2015; 15: 103.
- 12 Ayakaka I, Ackerman S, Ggita JM, *et al.* Identifying barriers to and facilitators of tuberculosis contact investigation in Kampala, Uganda: a behavioral approach. *Implement Sci* 2017; 12: 33.
- 13 Uganda Ministry of Health. Manual of the National Tuberculosis and Leprosy Programme. 2nd Edn. Kampala, Ministry of Health, 2010.
- 14 Uganda Ministry of Health. National HIV Testing Services Policy and Implementation Guidelines Uganda. 4th Edn. Kampala, Ministry of Health, 2016.
- 15 Ochom E, Meyer AJ, Armstrong-Hough M, *et al.* Integrating home HIV counselling and testing into household TB contact investigation: a mixed-methods study. *Public Health Action* 2018; 8: 72–78.
- 16 Uganda Ministry of Health. Uganda national policy guidelines for HIV voluntary counselling and testing. Kampala, Ministry of Health, 2005.
- 17 Ayakaka I, Ackerman S, Ggita J, *et al.* Designing an intervention to improve household TB contact investigation in Uganda. 9th Annual Conference on the Science of Dissemination and Implementation; Washington, DC, 2016.
- 18 Armstrong-Hough M, Ggita J, Turimumahoro P, *et al.* “Something so hard”: a mixed-methods study of home sputum collection for tuberculosis contact investigation in Uganda. *Int J Tuberc Lung Dis* 2018; 22: 1152–1159.
- 19 Meyer AJ, Babirye D, Armstrong-Hough M, *et al.* Text messages sent to household tuberculosis contacts in Kampala, Uganda: process evaluation. *JMIR Mhealth Uhealth* 2018; 6: e10239.
- 20 Armstrong-Hough M, Ggita J, Ayakaka I, *et al.* Brief report: “give me some time”: facilitators of and barriers to uptake of home-based HIV testing during household contact investigation for tuberculosis in Kampala, Uganda. *J Acquir Immune Defic Syndr* 2018; 77: 400–404.
- 21 Fair E, Miller CR, Ottmani SE, *et al.* Tuberculosis contact investigation in low- and middle-income countries: standardized definitions and indicators. *Int J Tuberc Lung Dis* 2015; 19: 269–272.
- 22 World Health Organization. *The End TB Strategy*. Geneva, World Health Organization, 2015.
- 23 Shelby T, Meyer AJ, Ochom E, *et al.* Social determinants of tuberculosis evaluation among household contacts: a secondary analysis. *Public Health Action* 2018; 8: 118–123.
- 24 Shapiro AE, van Heerden A, Schaafsma TT, *et al.* Completion of the tuberculosis care cascade in a community-based HIV linkage-to-care study in South Africa and Uganda. *J Int AIDS Soc* 2018; 21: <https://doi.org/10.1002/jia2.25065>.
- 25 Mhalu G, Hella J, Doulla B, *et al.* Do instructional videos on sputum submission result in increased tuberculosis case detection? A randomized controlled trial. *PLoS One* 2015; 10: e0138413.
- 26 Wald DS, Butt S, Bestwick JP. One-way versus two-way text messaging on improving medication adherence: meta-analysis of randomized trials. *Am J Med* 2015; 128: 1139, e1–e5.
- 27 Ngwatu BK, Nsengiyumva NP, Oxlade O, *et al.* The impact of digital health technologies on tuberculosis treatment: a systematic review. *Eur Respir J* 2018; 51: 1701596.
- 28 Gurol-Urganci I, de Jongh T, Vodopivec-Jamsek V, *et al.* Mobile phone messaging reminders for attendance at healthcare appointments. *Cochrane Database Syst Rev* 2013; 12: CD007458.
- 29 Ggita JM, Armstrong-Hough M, Katahoire A, *et al.* Experiences of household TB contacts with SMS results and instructions and influences on intentions to seek care. 49th Union World Conference on Lung Health; The Hague, The Netherlands, 2018.
- 30 Ggita JM, Ojok C, Meyer AJ, *et al.* Patterns of usage and preferences of users for tuberculosis-related text messages and voice calls in Uganda. *Int J Tuberc Lung Dis* 2018; 22: 530–536.
- 31 World Health Organization. Digital Health for the End TB Strategy: An Agenda for Action. Geneva, World Health Organization, 2015.
- 32 White EB, Meyer AJ, Ggita JM, *et al.* Feasibility, acceptability, and adoption of digital fingerprinting during contact investigation for tuberculosis in Kampala, Uganda: a parallel-convergent mixed-methods analysis. *J Med Internet Res* 2018; 20: e11541.
- 33 International Organization for Standardization. ISO 9241–210:2010—Ergonomics of human-system interaction—Part 210: Human-centred design for interactive systems. Geneva, International Organization for Standardization, 2010.
- 34 IDEO.org. The Field Guide to Human-Centered Design. San Francisco, 2015.
- 35 Bazzano AN, Martin J, Hicks E, *et al.* Human-centred design in global health: A scoping review of applications and contexts. *PLoS One* 2017; 12: e0186744.

- 36 Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011; 6: 42.
- 37 Curran GM, Bauer M, Mittman B, *et al.* Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care* 2012; 50: 217–226.
- 38 Cazabon D, Alsdurf H, Satyanarayana S, *et al.* Quality of tuberculosis care in high burden countries: the urgent need to address gaps in the care cascade. *Int J Infect Dis* 2017; 56: 111–116.
- 39 Floyd K, Glaziou P, Houben RMGJ, *et al.* Global tuberculosis targets and milestones set for definition and rationale. *Int J Tuberc Lung Dis* 2018; 22: 723–730.
- 40 Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; 8: 359–368.
- 41 Davis JL, Katamba A, Vasquez J, *et al.* Evaluating tuberculosis case detection *via* real-time monitoring of tuberculosis diagnostic services. *Am J Respir Crit Care Med* 2011; 184: 362–367.
- 42 World Health Organization. Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management. Geneva, World Health Organization, 2018.